CLINICAL RESEARCH PROTOCOL WHLS-005

TITLE: Effect of Frequent Daily Use of Microdent™ containing, Sorbitol-based, Sugar-free Mints in Reducing Dental Plaque Accumulation Between Brushings: A Double Blind, Cross-Over Treatment Design

CONDUCTED BY: Dr. Thomas Schiff, D.D.S.
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6/13/94
Signature of Responsible Party/Date

SPONSOR: Ira Hill, PhD
WhiteHill Oral Technologies, Inc.
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Hazlet, NJ 07730
(201) 264-0944

6/10/94
Signature of Responsible Party/Date

A. TITLE: Effect of Frequent Daily Use of Microdent™ containing, Sorbitol-based, Sugar-free Mints in Reducing Dental Plaque Accumulation Between Brushings: A Double Blind, Cross-Over Treatment Design

B. STUDY PRINCIPAL INVESTIGATOR: Thomas Schiff, D.D.S.

SPONSOR: Ira Hill, PhD
WhiteHill Oral Technologies, Inc.

C. STATEMENT OF PURPOSE:

The purpose of this clinical trial is to compare in normal human subjects the effect on dental plaque accumulation, between brushings, by multiple daily use of an ingestible sorbitol-based, sugar-free mint vs. a placebo mint without the active ingredient (trademarked Microdent™, a proprietary melt-emulsion of dimethicone* in a suitable poloxamer* which acts as an agent to both clean and modify the tooth surface free energy) .

*FDA reviewed Oral Care/Ingestible ingredients.

D. REVIEW OF THE LITERATURE:

1. General Overview of Plaque Formation and Effects, L. Menaker, Biologic Basis of Dental Caries, Chap. 5, 11, 12, 14, 16, 18., Harper and Row (1980)

2. Effect of Silicone (simethicone) on Alteration of Tooth Surface Energy and Plaque Attachment, Glanz (1969) and Baier and Glanz (1978))

3. Effect of silicone oil on protein adsorption to hydroxyapatite *in vitro* and on pellicle formation *in vivo*, M. Rykke and G. Rolla, *Scand J Dent Res*, 1990: **98**: 401-11.

4. Relevant Patents: U.S. Patent 4,950,479
"Method of Interrupting the Formation of Plaque"
(24 literature citations, 31 patent references)

U.S. Patent 4,911,927
"Method and Apparatus for Adding Chemotherapeutic Agents to Dental Floss"

E. EXPERIMENTAL DESIGN AND METHODS

1. Subject Selection

To participate in this clinical study, adults 18-65 years of age must meet the following criteria:

a. Excluding third molars, each subject must have at least 20 natural teeth present in the mouth.

b. Have no history of medications that are likely to effect gingival health, i.e. acute hormonal therapy, antisialagogues, and steroids. The use of prophylactic antibiotics or antibiotic usage during the two months preceding the study will be grounds for exclusion.

c. No medical history of rheumatic fever, AIDS, leukemia, cirrhosis, sarcoidosis, diabetes melitis, hepatitis, current pregnancy or any physical condition that limits manual dexterity.

d. A dental history that includes brushing the teeth at least once a day. Other reasons for exclusion are the presence of gross dental caries; gross neglect of oral hygiene; and the presence of advanced periodontitis, based on a non-invasive examination.

e. No orthodontic appliances or removable prosthesis.

f. Should not require premedication with antibiotics for dental appointments, including mitral valve click or other heart murmurs, heart valve replacement and artificial joint.

g. Sign a consent form.

h. At time of screening examination, the subject must have a Plaque Index score of at least 1.8 units (average of all surfaces scored). See Appendix A for criteria.

2. Screening Examination

After review of the subject's medical and dental history, the subject will be examined for a Plaque Index score of 1.8 units, or greater, (Turesky modification, 1970 of the Quigley-Hein criteria) using a disclosing solution.

3. Experimental Design

Twelve subjects will be selected from screening to assure at least 10 subjects/group at completion. This study will use a cross-over treatment design wherein the same subjects will be evaluated before and after using each of the products over two different 48-hour periods each. The treatment period will be across a four week period and consist of one experimental **test product** packaged in two separate sets of daily-use packets coded for use in a randomly selected sequence of weeks, and one identical-in-appearance-and-taste **placebo product** similarly packaged and code labeled.

The use of each product by the same subjects on two separate weeks produces an effective cell size of 20-24 subjects, further amplified by the cross-over design which allows each mouth to effectively serve as its own control.

A prior series of "range-finding" clinical trials established that this protocol and several formula variants of the selected **test product** demonstrated a reduction in plaque accumulation of about 20% vs. the **placebo** which was statistically significant with only 10 subjects in the cross-over design.

The "accumulation between brushings" effect will be evaluated by instructing the subjects to follow normal oral hygiene during each weekly period, *except* for the 48 hour product-use period. During the 48 hour product-use period, the only oral hygiene use permitted is the slow dissolution in the mouth of the indicated mint product at six prescribed times of (1)after each meal, (2) once between each meal and (3) at bedtime.

Plaque accumulation scoring will be performed by only one examiner (The Principle Investigator) throughout the study on a blind basis.

Assessment of plaque accumulation will be made at a baseline examination at the beginning of each week. Each subject will then be given a supragingival, rubber-cup prophylaxis to bring the starting plaque score to zero and product for use over the next 48 hours distributed with instructions. At the end of each 48 hour, no-brushing, product-use period for each subject the plaque scores will be assessed for the "final" reading on that week's product. Baseline and final examination will be performed within the same one-hour time period of the respective day.

4. Protocol

Patients will be instructed to brush their teeth according to their normal oral hygiene patterns, using only the brush and toothpaste provided, except for the specified 48-hour product-use period.

SCHEDULE

WEEK ONE

T = 0 HOURS

Subjects have refrained from brushing 12 hours before Baseline Scoring. — BASELINE EXAMINATION

Perform a standard rubber cup prophylaxis to reduce initial plaque index to zero. — PROPHY

Subjects are given two coded packets containing six of the appropriate product mints and instructed as to use.

Subjects are instructed to use no other oral hygiene products or procedures over the next 48 hours.

T = 48 HOURS

Subjects have used specified product as sole oral hygiene since last brushing. — FINAL EXAMINATION

Subjects are instructed to return to their normal oral hygiene procedures for the remainder of the week.

WEEK TWO

Repeat exactly Week One

WEEK THREE

Repeat exactly Week One

WEEK FOUR

Repeat exactly Week One

TIMES OF USE

1. After breakfast (if no meal taken then by 9 a.m. each day)
2. Mid-morning (if mid-morning snack is taken, immediately after snack)
3. After lunch (if no meal taken then between 12 noon and 1 p.m.)
4. Mid-afternoon (if mid-afternoon snack is taken, immediately after snack)
5. After dinner (if no meal taken, then between 6 and 7 p.m.)
6. Just before retiring (after all evening snacks are completed)

Compliance will not be monitored, but patients will be instructed to return all used product packets.

The clinical coordinator will provide each subject with two appropriate envelopes (one for each day), marked with the appropriate code for that particular week of the study. The Sponsor is responsible for breaking the code and examining returned product containers.

5. Subject Protection/Liability

Since the procedures to which subject volunteers will be exposed are no different from those ordinarily used by each clinical site in routine evaluation and treatment of patients, the patient protection measures ordinarily employed by each clinical site with respect to prospective and accepted patients are sufficient. Informed consent of each subject accepted into the study will be recorded on a form customarily used by that clinical site and acceptable to its I.R.B. (See Appendix E-H). This will be included in the subject's clinical file along with his/her medical history form and data collected in the course of the study. Patients will be remunerated as deemed appropriate by the clinical site.

6. Principal Investigator's Duties

The Principal Investigator shall manage the study at his site to provide for proper blinding, orderly and professionally responsible handling of subjects and tests or examinations, accurate compilation of data, timely and accurate reporting to the Sponsor, and protection of Subjects' rights.

7. Monitoring

Employees, consultants, or other appropriately qualified agents of the Sponsor shall monitor the activities at each clinical site to assure adherence to the protocol and protection of subjects' rights.

8. Data Analysis

Appropriate statistical methods will be employed by an independent, qualified Biostatistician, whose services will be contracted for by the Sponsor, to evaluate correlations among the parameters of the study. At minimum, correlations between plaque accumulation means and individual deltas according to treatment will be determined. For purposes of establishing cell size, the data for the two weeks utilizing the same product will be combined into the **placebo** or **test product** groups respectively. Other exploratory analyses will also be made.

APPENDIX A

Turesky Modification of Quigley Hein Plaque Scoring Method

0 = No plaque.

1 = Separate flecks of plaque at the cervical margin of the tooth.

2 = A thin continuous band of plaque (up to one mm) at the cervical margin of the tooth.

3 = A band of plaque wider than one mm but covering less than one-third of the Crown of the tooth.

4 = Plaque covering at least one-third but less than two-thirds of the crown of the tooth.

5 = Plaque covering two-thirds or more of the crown of the tooth.

1. Quigley GH & Hein JW JADA 65:26, 1962
2. Turesky, S. et. al. J. Periodont 41:41, 1970

If fleck of plaque (line angles or anywhere) is NOT in contact with gingiva - score it ZERO.

If it CONTACTS gingiva - same fleck is scored 1.

If 1 mm or less band but with small break - Score 2.

If any portion of band has area of more than 1 mm and/or less than 1 mm although it is not a continuous band (see illustration below) - score it 3.

APPENDIX B

STUDY QUESTIONNAIRE

PLEASE PRINT

Name_____

Telephone(Office)_____ (Home)_____

Office/Lab Address: _____ (Room)_____

Social Security #_____

Home Address: (Street) _____

(City) _____

(State & ZIP)_____

Gender (sex) _____

Age _____

Race _____

How many times per day do you brush? _____

Have you ever had a heart murmur? Yes_____ No_____

Have you ever had hepatitis? Yes_____ No_____

Do you have diabetes? Yes_____ No_____

Are you currently pregnant? Yes_____ No_____

APPENDIX C

University of the Pacific School of Dentistry
Informed Consent - BreathMint Study

If accepted for this study, you will participate in a four week investigation of the efficacy of a breathmint on reducing plaque accumulation between brushing. The breathmint contains only ingredients that are commercially available and FDA approved. You are asked to participate because you are an apparently health adult with most of your natural teeth. You must come each week for two examinations - at the beginning and again 48 hours. A tooth cleaning will be performed just after the first examination. The teeth and gums will be examined and a removable stain to disclose plaque (germs) will be applied to the teeth. It is estimated each examination will require 10-15 minutes. You will use the breathmints in a normal fashion 6 times a day at home during the forth-eight hour test period. At the conclusion of the four week study you will be paid $100, provided you miss no appointments **and return all the unused breathmints and packets at the end of the study.**

Assignment of products each week will be made on a random basis. During the remainder of each week between the **product-use period,** you will brush as you have always done but you cannot use a therapeutic mouthrinse. Routine dental treatment, other than cleanings, may be done during the four weeks of the study.

You should report to us any antibiotics or other prescription drugs taken during the study.

Your decision not to participate in the study or to withdraw after the study starts will not prejudice your future relations with the University of the Pacific School of Dentistry.

Your signature below indicates that you understand that UOP has made no provision for monetary compensation to you in the event of physical injury resulting from the research procedures. Should physical injury occur, medical treatment is available, but treatment is not provided free of charge.

If you have any question, we expect you to ask us. If you have additional questions later, Dr. Schiff can be reached at the Department of Radiology, University of the Pacific School of Dentistry.

You are making a decision whether or not to participate. Your signature indicates you have decided to participate after having read the information above.

Signature_____ Date_____

Signature of Investigator_____

APPENDIX D

BUDGET FOR WHLS-005

SUBJECT FEES	12 X $120	$1440.00
DENTAL HYGIENIST(S)	48 X $60	$2880.00
DENTAL ASSISTANT AND DATA RECORDER		$2000.00
SECRETARIAL SERVICES		$1000.00
PROJECT COORDINATION		$1500.00
SUPPLIES AND CONSUMABLES		$1250.00
FACULTY SALARY OFFSET		$4000.00
SUB-TOTAL		$14,070.00
INSTITUTIONAL OVERHEAD @ 44%		$6190.00
TOTAL DUE UNIVERSITY OF THE PACIFIC SCHOOL OF DENTISTRY		$20,260.00

PAYMENT SCHEDULE

DUE UPON APPROVAL OF PROTOCOL est to be July 1, 1994	$10,260.00
DUE UPON RECEIPT OF ALL DATA SHEETS and SUMMARY OF CONCLUSIONS BY PRINCIPLE INVESTIGATOR	$10,000.00

APPENDIX E

RESEARCH AGREEMENT

Between

WHITEHILL ORAL TECHNOLOGIES, INC.

And

UNIVERSITY OF THE PACIFIC SCHOOL OF DENTISTRY

THIS RESEARCH AGREEMENT, made this day, by and between WhiteHill Oral Technologies, Inc. (hereinafter referred to as "the Sponsor") and the University of the Pacific School of Dentistry (hereinafter referred to as "the University").

NOW THEREFORE, THE PARTIES HERETO AGREE AS FOLLOWS:

ARTICLE I: STATEMENT OF WORK. The University agrees to use its best efforts to perform the research program entitled "Effect of Frequent Daily Use of Microdent™ containing, Sorbitol-based, Sugar-free Mints in Reducing Dental Plaque Accumulation Between Brushings " as set forth in the Protocol which is attached to this Agreement as Exhibit "A".

ARTICLE II: PRINCIPAL INVESTIGATOR. The research will be supervised by Dr. Thomas Schiff. If, for any reason, Dr. Schiff is unable to serve as Principal Investigator, and a successor acceptable to both the University and the Sponsor is not available, this Agreement shall be terminated as provided in Article VI.

ARTICLE III: PERIOD OF PERFORMANCE. The performance of this Agreement shall begin July 1, 1994, and shall not extend beyond the estimated completion date of September 1, 1994, unless the period is further extended by amendment to this Agreement. However, the University shall have no liability to Sponsor, nor shall it be in default under this agreement if performance is delayed or prevented by any cause beyond the University's control.

ARTICLE IV: REIMBURSEMENT OF COSTS. In consideration of the foregoing, the Sponsor will reimburse the University for all costs (direct and indirect) incurred in the performance of the research which shall not exceed the total estimated project cost of $20,260 without written authorization from the Sponsor.

ARTICLE V: PAYMENT. Payments shall be made to the University by the Sponsor in advance on the following schedule:

1. $10,260 payable by July 1, 1994; and
2. Balance ($10,000) payable after submission of final data sheets and conclusions by principle investigator.

ARTICLE VI: TERMINATION. Performance under this Agreement may be terminated by the Sponsor upon sixty (60) days written notice; performance may be terminated by the university if circumstances beyond its control preclude continuation of the research. Upon termination, the University will be reimbursed as specified in Article IV for all costs and non-cancelable commitments incurred in the performance of the research prior to the termination date of the Agreement. Such reimbursement is not to exceed the total estimated project cost specified in Article IV.

ARTICLE VII: PUBLICATIONS. The University will be free to publish papers dealing with the results of any research under this Agreement. Where appropriate the University will give a copy of the paper to the Sponsor at least thirty (30) days prior to the intended submission for publication to allow the Sponsor to review for patent purposes and/or for inadvertent disclosure of the Sponsor's proprietary data.

ARTICLE VII: SPONSOR PROPRIETARY DATA. The free dissemination of information is an essential and long-standing policy of the University. However, under exceptional circumstances, the University recognizes that it may properly hold in confidence data supplied by a sponsor which the University considers essential for the conduct of a research program. Accordingly, the University's acceptance and use of any proprietary data which may be supplied by the Sponsor in the course of this research project shall be subject to the following:

(a) The data must be marked or designated in writing as proprietary to the Sponsor.

(b) The University retains the right to refuse to accept any such data.

(c) Where the University does accept such data as proprietary, it agrees to exercise all reasonable efforts not to publish or otherwise reveal the data to others without the permission of the Sponsor, unless the data has already been or is subsequently published or disclosed publicly by third parties, was previously known or subsequently independently discovered by the University without the benefit of the proprietary data, or is required to be disclosed by order of a court of law or other governmental authority. It is agreed that such reasonable efforts by the University or other governmental authority will be in lieu of all other obligation or liabilities of the University relative to proprietary

ARTICLE IX: PATENTS. Title to any invention or discovery made or conceived by University personnel in the performance of the research shall remain with the University provided, however, that the University shall grant to the Sponsor the rights of first negotiation to obtain a license to make, use, and/or sell such invention or discover, with the right to sublicense, under reasonable terms. The terms of exclusivity, fees and royalty rates will be negotiated with the University at the time the invention or discovery is make, provided further, however, that this right must be exercised by the Sponsor by notice in writing to the University within three (3) months from the date the invention or discovery is first disclosed to the Sponsor.

If the University files patent applications or otherwise obtains patent rights which relate to the licensed products of this Agreement, and if the Sponsor shall obtain rights to a further option or a license under such patent rights as are set forth in this section, the Sponsor shall bear the reasonable costs for the preparation, filing and prosecuting of the patent applications under which the Sponsor accepts a license, but in no case beyond an appeal to and a decision by the United States Patent and Trademark Office Board of Appeals, unless the Sponsor specifically agrees otherwise in writing.

ARTICLE X: USE OF NAMES. Neither party will use the name of the other nor the name of any of its employees in any form of publicity without the written permission of the other. In the case of the University, permission of the University Relations Office is required.

ARTICLE XI: ASSIGNMENT. Neither this Agreement nor the rights herein granted to the University shall be assignable or otherwise transferrable by the University without the Sponsor's prior written consent, except that the University may assign or otherwise transfer this Agreement or the rights granted herein to a University-related, non-profit research foundation. Such assignment shall not relieve the University of its obligations hereunder and the Sponsor may ask for reasonable assurances to such effect. Any such assignee for the University shall be bound by the terms hereof as if such assignee were the original party hereto.

ARTICLE XII: INDEPENDENT CONTRACTOR. In the performance of this agreement the University shall be an independent contractor. Neither party is authorized to act as the agent for the other and neither shall be bound by the acts of the other.

ARTICLE XIV: APPLICABLE LAW. This agreement shall be governed by the laws of the State of California.

UNIVERSITY OF THE PACIFIC
SCHOOL OF DENTISTRY

BY _____ 6/13/94
Dr. Thomas Schiff (date)

WHITEHILL ORAL
TECHNOLOGIES, INC.

BY _____ 6/10/94
Dr. Ira Hill (date)

WhiteHill Oral Technologies, Inc.

Ira Hill, PhD *732-291-3857 voice*
10 Clay Court *732-291-4101 fax*
Locust, NJ 07760 *dochill@monmouth.com*

CLINICAL RESEARCH PROTOCOL WHLS-005

SPONSOR'S DECODE

High Viscosity Polydimethylsiloxane (PDMS) Melt-emulsions in Sugar-free Mints Trials
Planters/Lifesavers

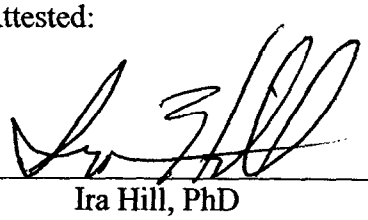
#111 = Placebo (Sorbitol based mint, same flavor and size, no melt emulsion)

#444 = 1.5% melt-emulsion of 90% Poloxamer 407 and 10% PDMS (600,000 cs viscosity)

#555 = 1.5% melt-emulsion of 90% Poloxamer 407 and 10% PDMS (2,500,000 cs viscosity)

#666 = 1.5% melt-emulsion of 95% Poloxamer 407 and 5% PDMS (2,500,000 cs viscosity)

Attested:



Ira Hill, PhD

7/15/94

date